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(54) SYSTEME POUR CONSERVER LES PREPARATIONS OPHTALMIQUES
(54) PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

(57)

Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COON group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthamologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. The ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.

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(54) **SYSTEME POUR CONSERVER LES PREPARATIONS OPHTALMIQUES**

(54) **PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS**

(57) Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COOH group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthamologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. The ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.

ABSTRACT OF THE DISCLOSURE

Stable, clear, antimicrobially effective, ophthalmic formulations are disclosed which provide an antimicrobially effective preservative. The formulations include an ophthalmologically effective amount of a drug, which is a -COOH group-containing non-steroidal anti-inflammatory drug (NSAID) in combination with an antibiotic drug, and a preservative system formed of a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle. The preservative system can be used with other formulations which require the preservative to be ophthamologically acceptable and antimicrobially effective. These formulations are useful for treating diseases and/or conditions that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. The ophthalmologically acceptable antibiotic is preferably tobramycin which has been found not to interfere with the rate of diffusion of the NSAID. The combination of the NSAID and antibiotic is particularly effective in simultaneously preventing and/or eliminating infection while preventing and/or eliminating inflammation.

PRESERVATIVE SYSTEM FOR OPHTHALMIC FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to improved ophthalmic formulations which use an improved preservative system comprising a quaternary ammonium preservative and a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant for ophthalmic formulations of carboxyl ("-COOH") group-containing non-steroidal anti-inflammatory drugs ("NSAIDs") and contain an opthalmologically acceptable antibiotic, preferably tobramycin. The invention also relates to methods of using these formulations for treating diseases and/or conditions that are either caused by, associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury. In addition, the formulation can be used to treat bacterial infection.

BACKGROUND OF THE INVENTION

To be ophthalmologically acceptable, a formulation must possess a number of characteristics to comply with

the general FDA requirements of being safe and effective. In that eyes are quite sensitive to pain, the formulation must be developed such that it causes little to no discomfort or stinging when administered. This feature is particularly important to insure user compliance and important in that such formulations are often administered in order to relieve pain or inflammation. The ophthalmic use of NSAID compounds was disclosed in U.S. Patent No. 4,454,151, where NSAID compounds (such as those described in U.S. Patents 4,089,969; 4,232,038; 4,087,539 and 4,097,579) were exemplified in formulation with $NaH_2PO_4"H_2O$, $Na_2HPO_4"H_2O$, NaCl, benzalkonium chloride ("BAC") and sterilized water. While the formulations described in the '151 patent were efficacious, a complex was found to form between the NSAID and the BAC.

Due to the formation of this complex, the formulations did not have the stability desired for shelf life in commercial applications. A reasonable minimum shelf life is at least about one year, representing sufficient time to package, ship, and store a formulation without having to replace expired stock too frequently.

An ophthalmic suspension containing a particular NSAID is disclosed in U.S. Patent No. 4,087,538 issued May 2, 1978. The suspension is aqueous based and can include benzalkonium chloride. Another ophthalmic formulation is disclosed in U.S. Patent No. 4,559,343 issued December 17, 1985. The formulation is aqueous based and includes an NSAID and a benzalkonium chloride preservative. A somewhat similar ophthalmic formulation is disclosed in U.S. Patent No. 4,607,038 issued August 19, 1986. This formulation includes a specific NSAID (pranoprofen) in an aqueous based formula with a known

preservative. U.S. Patent No. 4,474,751 issued October 2, 1984 discloses ophthalmic formulations which gel in the eye in order to increase the bioavailability of the drug. The '751 patent discloses a large number of different active ingredients and excipient material. When this disclosure is taken in view of the other patents discussed above and the publications cited in each of them, the vast number of different ways of creating an ophthalmic formulation becomes apparent. Although there may be a considerable number of possible formulations and variations thereof, only certain specific formulations will meet all the requirements for being ophthalmologically acceptable.

In general, an ophthalmic formulation contains an active compound and various ophthalmologically acceptable excipients, in the form of a solution, an ointment, a suspension, etc. In order for an excipient to be ophthalmologically acceptable, it must be non-irritating to the eye in combination with other excipients and an active ingredient. The excipients must not prevent the active ingredient from penetrating the blood-aqueous barrier and/or diffusing through the various ocular substructures to the site where it is pharmacologically active. The excipients can interact with each other or the active drug. Accordingly, care in formulating is required in that so many materials may be used. These materials generally include a tonicifier, a preservative, a surfactant, a buffering system, a chelating agent, a viscosity agent as well as other stabilizing agents. Ophthalmic formulations must be sterile and must be preserved with an effective anti-microbial agent.

Organo-mercurials (e.g., thimerosal, phenylmercuric acetate and phenylmercuric nitrate) have been used extensively as the preservative in ophthalmic

solutions. These compounds, however, pose difficulties due to potential mercury toxicity as well as poor chemical stability. Benzalkonium chloride, a quaternary ammonium compound, has been widely used in ophthalmic solutions, and is considered to be the preservative of choice. However, BAC has typically been considered to be incompatible with anionic drugs (e.g., salicylates or nitrates, etc.) and can be inactivated by surfactants.

Many NSAIDs (such as ketorolac, indomethacin, flurbiprofen, diclofenac, and suprofen) are being developed for ocular use because of their activity as anti-inflammatory agents as well as their ability to prevent cystoid macular edema.

These NSAIDs have proven to be incompatible with quaternary ammonium compounds such as BAC because they can form a complex with them, rendering the preservative less available to serve its function, as is the case with other ophthalmic drugs that contain a -COOH group. Thus, less preferred preservatives have been used in such ophthalmic formulations. For example, Ocufen Ophthalmic solution, the first NSAID (flurbiprofen) approved by the FDA for ophthalmic use, incorporates thimerosal (with EDTA) as its preservative system.

European published application 306,984 (published March 15, 1989) discloses a stable, clear, antimicrobially effective, ophthalmic formulation containing an NSAID and a preservative system formed of a quarternary ammonium preservative and a nonionic surfactant all in an aqueous vehicle. Although the formulations of this European laid-open application are useful in treating diseases that are either caused by, associated with, or accompanied by inflammatory processes, there is no indication that the formulations of the European laid-open application are effective inpreventing or eliminating infection.

A need has continued to exist for a stable, clear, antimicrobial preservative effective ophthalmic formulation for NSAIDs with antibiotics using BAC as the preservative, and an improved preservative system for -COOH group containing ophthalmic drugs to overcome both inflammation and infection.

SUMMARY OF THE INVENTION

A primary object of the invention is to describe and disclose a formulation containing an ophthalmologically effective amount of an NSAID in combination with an antibiotic, a quaternary ammonium preservative and a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant, all in an aqueous vehicle.

A feature of the present invention is that it allows for the preparation of stable, i.e., clear and antimicrobially and antibiotically effective, NSAID-containing ophthalmic formulations without the need for an organo-mercurial preservative.

Another feature is that methods for treating ophthalmic diseases in mammals using the ophthalmic pharmaceutical formulations of the invention are provided.

An advantage of the present invention is that it is useful in the treatment of diseases or conditions associated with or accompanied by inflammatory processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury and eliminating infection.

These and other objects, advantages and features of the present invention will become apparent to those persons skilled in the art upon reading the details of the composition, manufacture and usage as more fully set forth below. Reference being made to the accompanying

general structural formulae forming a part hereof wherein like symbols refer to like molecular moieties throughout.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

Before the present compositions and processes for making and using such are disclosed and described, it is to be understood that this invention is not limited to the particular compositions, components or methods of use described as such compositions, components and methods may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting since the scope of the present invention will be limited only by the appended claims.

It must be noted that as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutically acceptable salt" includes mixtures of salts, references to "an NSAID" includes reference to mixtures of such NSAIDS, reference to "the method of administration" includes one or more different methods of administration known to those skilled in the art.

Definitions

As used herein, the term "NSAID" means an ophthalmologically acceptable carboxyl group containing non-steroidal anti-inflammatory drug. The NSAID's include, for example, flurbiprofen, ketorolac, diclofenac, indomethacin, suprofen, and the isomers, esters and pharmaceutically acceptable salts thereof.

As used herein, the term "q.s." means adding a

quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

As used herein, the term "treatment" or "treating" means any treatment of a disease and/or condition in a mammal, including:

(i) preventing the disease and/or condition, that is, causing the clinical symptoms of the disease not to develop;

(ii) inhibiting the disease and/or condition, that is, arresting the development of clinical symptoms; and/or

(iii) relieving the disease and/or condition, that is, causing the regression of clinical symptoms.

As used herein, the term "effective amount" means a dosage sufficient to provide treatment for the disease state being treated. This will vary depending on the patient, the disease and the treatment being effected.

As used herein, the term "antimicrobially effective" refers to the stability of the formulation prior to administration and means ability to withstand the U.S. Pharmacopia antimicrobial challenge put by a panel of microbes.

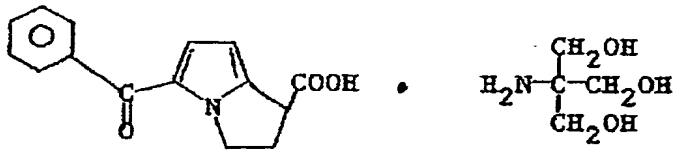
As used herein, the term "surfactant" means a nonionic surfactant, preferably ethoxylated octylphenol compounds as described below.

As used herein, the term "quarternary ammonium preservative" means a quarternary ammonium compound as described below.

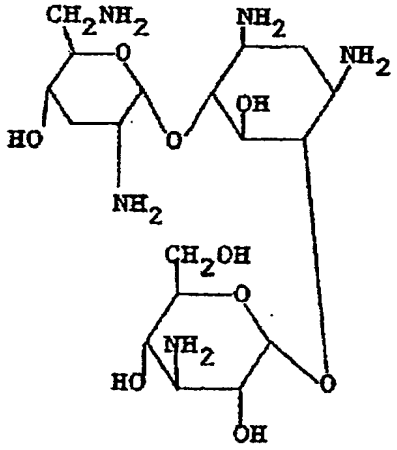
As used herein, the term "stabilizing" means keeping a formulation clear and antimicrobially effective for its minimum reasonable shelf life, e.g., at least one year.

"Ketorolac tromethamine" shall mean the compound (±)-5-benzoyl-1,2-dihydro-3H-pyrrolo-[1,2-a]-pyrrole-1-carboxylic acid 2-amino-2-hydroxymethyl-1,3-propanediol

salt, also known as (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) having the following structural formula (1)



"Tobramycin" shall mean the antibiotic produced by Streptomyces tinebrarius also known as O-3-amino-3-deoxy-a-D-glucopyranosyl-(1$6)-O-[2,6-diamino-2,3,6-trideoxy-a-D-ribo-hexopyranosyl-(1$4)]-2-deoxy-D-streptamine. Tobramycin is represented by the following structural formula II:



Tobramycin is a water soluble aminoglycosidic antibiotic having a broad spectrum of action against both gram negative and gram positive bacteria. Such

aminoglycosidic antibiotics are useful in treating ocular infections and are used prophylactically before and after ocular surgery.

Formulations

The formulations of the present invention include an NSAID active agent in an effective amount for ophthalmic treatment, an ophthalmologically acceptable antibiotic as a second active agent in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant, optionally including other excipients such as a chelating agent, a tonicifier, a buffering system, a viscosity agent as well as other stabilizing agents.

The NSAID is preferably flurbiprofen, ketorolac, diclofenac, indomethacin, suprofen, and the isomers, esters, and pharmaceutically acceptable salts thereof. The antibiotic is preferably tobramycin.

Ophthalmic solutions and suspensions typically contain an aqueous vehicle rather than an oily vehicle. Ophthalmic formulations must be sterile, and if intended for multiple dosing regimens, must be antimicrobially effective for their minimum reasonable shelf life, e.g., at least one year, and preferably two to three years or more. The ingredients used in the formulations of the present invention are typically commercially available or can be made by methods readily known to those skilled in the art.

Pharmaceutical ophthalmic formulations typically contain an effective amount, e.g., 0.001% to 10% wt/vol., preferably 0.002% to 5% wt/vol, most preferably 0.005% to 1% of an active ingredient (e.g., the NSAID of the present invention). The amount of active ingredient will vary with the particular formulation and the disease state for which it is intended. The total

concentration of solutes should be such that, if possible, the resulting solution is isotonic with the lacrimal fluid (though this is not absolutely necessary) and has a pH in the range of 6 to 8.

The formulations of the present invention are prepared as solutions incorporating the above-described ingredients within the following approximate ranges:

Ingredient	Amount
Active Agent*	0.001% to 10.0% wt/vol.;
Preservative	0.001% to 1.0% wt/vol.;
Surfactant	0.001% to 1.0% wt/vol.;
Other Excipients	0% to 10.0% wt/vol.; and
Purified Water	q.s. to 100%.

*The active agent is the NSAID in combination with the antiobiotic.

Optional other excipients, such as a chelating agent and a tonicifier, are used in the following approximate proportions:

Ingredient	Amount
Chelating agent	0.01% to 1.0%wt/vol.;
Tonicifier	q.s. to achieve isotonicity with lacrimal fluid; and
1N NaOH or 1N HCl	q.s. to adjust pH to 6.0 to 8.0.

In a preferred ophthalmic NSAID solution, the ingredients are combined in the following proportions:

Ingredient	Amount
NSAID	0.50% wt/vol.;
Antibiotic	0.30% wt/vol.;
BAC (50% aq. soln.)	0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
NaCl/ boric acid/ Na borate	q.s. for isotonicity with lacrimal fluid;
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

The invention relates primarily to formulations having as the active agent ophthalmologically acceptable drugs (including the esters and pharmaceutically acceptable salts thereof) that can form a complex with a quaternary ammonium compound, particularly carboxyl group-containing NSAIDs.

NSAIDs useful in the practice of this invention include, for example, ketorolac (and the other compounds described as being ophthalmologically effective in U.S. Patent No. 4,454,151 to Waterbury, issued June 12, 1984, the pertinent portions of which are incorporated herein by reference), indomethacin, flurbiprofen sodium, diclofenac, and suprofen, including the esters and pharmaceutically acceptable salts thereof.

In addition to the NSAID there is another active ingredient in the form of an ophthalmologically acceptable antibiotic, preferably tobramycin. The antibiotic is present in an effective amount for ophthalmic treatment. The antibiotic tobramycin does not interfere with the corneal permeability of the NSAID.

Preservatives useful in the formulations of the present invention include quaternary ammonium compounds, such as cetyltrimethylammonium bromide, cetylpyridinium chloride and preferably, benzalkonium chloride.

The nonionic surfactants useful in the formulations of the present invention are preferably polyoxyethylated octylphenol surfactants including polyoxyethylene hydrogenated vegetable oils, such as polyethylene 60 hydrogenated castor oil, manufactured and sold by Kao Corp. of Japan under the trade name Emanon CH-60, and preferably ethoxylated octylphenol compounds, such as Octoxynol 10 and most preferably Octoxynol 40, manufactured and sold by GAF under the trade name Igepal CA897 (a 70% aqueous solution of Octoxynol 40). Octoxynol 40 is a nonionic polymeric surfactant material. More specifically, it is a nonionic polyoxyethylated octylphenol surfactant material sold commercially by GAF.

Among the optional excipients, the chelating agents useful in the formulations of the present invention include 8-hydroxyquinoline sulfate, citric acid, and preferably disodium edetate. Under certain conditions, the chelating agent may also enhance the anti-microbial effect due to its ability to render essential metal ions unavailable to the microbes.

Buffering systems optionally useful in the formulations of the present invention are based on, for example, citrate, borate, or phosphate.

Tonicifiers optionally useful in the formulations of the present invention include dextrose, potassium chloride and/or sodium chloride, preferably sodium chloride.

Viscosity agents optionally useful in the formulations of the present invention include the cellulose derivatives such as hydroxypropylmethyl

cellulose, sodium carboxymethylcellulose, and hydroxyethylcellulose.

Other optional excipients useful in the formulations of the present invention include stabilizing agents such as antioxidants, e.g., sodium metabisulfate and ascorbic acid, depending on the NSAID used.

These formulations are prepared by dissolving the solutes (e.g., the NSAID, the preservative, the surfactant, the chelating agent, and the buffering agent) in a suitable quantity of water, adjusting the pH to about 6 to 8, preferably 6.8 to 8.0 and most preferably 7.4, making a final volume adjustment to 100% with additional water, and sterilizing the preparation using any suitable method known to those in the art.

Ophthalmic formulations incorporating the preservative system of the invention are physically stable (i.e., remain clear) and functionally stable (i.e., remain antimicrobially effective) for at least the minimum reasonable shelf life of such products. The inclusion of an antibiotic in the formulation does not effect the rate of diffusion of the NSAID.

Preferred Formulations

The preferred ophthalmic formulation of the invention includes a NSAID active agent in an effective amount for ophthalmic treatment and an antimicrobially effective amount of the above-described preferred preservative system.

The preferred preservative of the invention is benzalkonium chloride.

The preferred surfactant of the invention is Octoxynol 40, especially when combined with benzalkonium chloride.

The preferred chelating agent of the invention is disodium edetate, especially when combined with benzalkonium chloride and Octoxynol 40.

The preferred antibiotic is one which does not interfere with the corneal permeability of the NSAID. Tobramycin is a preferred antiobiotic.

The preferred ophthalmic solutions of the invention include a NSAID, benzalkonium chloride, Octoxynol 40 and disodium edetate and, as a second active agent, tobramycin.

A preferred ophthalmic NSAID/antibiotic solution has the following formulation:

Ingredient	Amount
NSAID	0.50% wt/vol.
antibiotic	0.30% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
(NaCl/boric acid/ Na borate)	q.s. for isotonicity with lacrimal fluid
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4±0.4
Purified Water	q.s. to 100%

Most preferred is the ophthalmic solution according to the above formulations is wherein the NSAID is Ketorolac Tromethamine and when the antibiotic is present it is tobramycin.

Utility and Administration

This invention is directed to NSAID ophthalmic formulations and a method useful for treating ophthalmic diseases in mammals. These diseases are either caused by, associated with or accompanied by inflammatory

processes, including, among others, glaucoma, cystoid macular edema, uveitis, diabetic retinopathy and conjunctivitis, or any trauma caused by eye surgery or eye injury.

The method of this invention is both curative and preventative. Where applied, for example, pre-surgically or immediately post-traumatically, i.e. before inflammation develops, it prevents development of inflammation. When applied directly to the eye suffering from any of the named ophthalmic diseases, it supresses already developed inflammatory processes.

The formulation of the invention includes an antibiotic such as tobramycin, providing antibacterial properties useful in eliminating and/or preventing a bacterial infection.

Ophthalmic formulations are typically administered by topical application to the eyelids or for instillation into the space (cul-de-sac) between the eyeball and the eyelids, by topically applied ophthalmic solutions, suspensions or ointments, or by subconjunctival injection.

The dosage level will, of course, depend on the concentration of the drops, the condition of the subject and the individual magnitude of responses to treatment. However, typical dosage ranges might be about 2 to 10 drops of solution of active ingredient per day wherein the solution includes 0.5 wt/vol.% of Ketorolac trimethamine and 0.3 wt/vol.% of tobramycin.

For a more detailed discussion of ophthalmic formulations, their preparation and administration, see Remington's Pharmaceutical Sciences, 15th Ed., pages 1489-1504, (1975).

Testing

Ophthalmic formulations such as the solutions of

the present invention are typically tested for physical stability, chemical stability, and preservative efficacy, both when they are first manufactured and after a fixed period of time (e.g., after two years). They are generally considered to be safe and clinically acceptable if proven to be well tolerated in the eye.

Physical stability is determined by observation of a solution after expiration of a fixed period of time. A solution is considered to be physically stable if its appearance (e.g., color and clarity) does not change and if the pH remains constant, within acceptable limits. Chemical stability involves a routine chemical analysis of the solution, to be sure that its active ingredient(s), preservatives and the excipients have not changed after a fixed period of time.

Preservative efficacy of the formulation prior to administration is tested by the procedure described in the U.S. Pharmacopia Compendiary, whereby a solution is challenged with a panel of microbes and a determination is made as to whether a given microbe survives in it.

EXAMPLES

The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as a limitation on the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID Ketorolac

Tromethamine and the antibiotic tobramycin.

Ingredient	Amount
ketorolac tromethamine	0.50% wt/vol.
tobramycin	0.30% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4%0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 2

This example illustrates the preparation of a general pharmaceutical formulation for ophthalmic

administration containing an NSAID and an antibiotic.

Ingredient	Amount
NSAID	0.50% wt/vol.
antibiotic	0.3% wt/vol.
BAC (50% aq. soln.)	0.01% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.02% wt/vol.
EDTA Na_2	0.20% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.

EXAMPLE 3

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID ketorolac tromethamine and tobramycin.

Ingredient	Amount
ketorolac tromethamine	0.50% wt/vol.
tobramycin	0.30% wt/vol
BAC (50% aq. soln.)	0.01% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.20% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.

Other NSAIDs, such as those described above, can be used as the active compound in the preparation of the

formulation of any of these examples.

EXAMPLE 4

This example illustrates the preparation of a representative pharmaceutical formulation for ophthalmic administration containing the NSAID flurbiprofen sodium.

Ingredient	Amount
Flurbiprofen Sodium	0.03% wt/vol.
BAC (50% aq. soln.)	0.02% wt/vol.
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.
EDTA Na_2	0.10% wt/vol.
NaCl	0.18% wt/vol.
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.

The above ingredients are mixed, adding purified water until they are dissolved, the pH is adjusted to 7.4%0.4 and the balance of the formulation is made up with purified water, adding a quantity sufficient to make 100% volume. The solution is then sterilized.

Other ophthalmic drugs and NSAIDs, such as those described above, can be used as the active compound in the preparation of the formulation of this example.

EXAMPLE 5

Physical stability of the formulations of the present invention is measured by preparing clear formulations, e.g., according to the foregoing Examples, sealing them in sterilized containers, and observing the clarity of the solution after a period of one month and again after five months. Solutions that remain clear are considered stable in this procedure.

The formulations of the present invention have proven to be stable when tested in accordance with the above procedure. Formulations using surfactants other than the nonionic surfactants of the invention did not remain clear and were not stable.

Preservative efficacy of the formulations of the present invention is measured by preparing formulations, e.g., according to the foregoing Examples, and subjecting them to the U.S. Pharmacopia antimicrobial challenge.

The formulations of the present invention demonstrate preservative efficacy when tested in accordance with the above procedure.

Formulations of the present invention are freely flowable liquids which can be administered directly to the eye using a conventional means such as eyedroppers. The amount of active ingredient administered will vary with the individual and/or the type of disease or condition being treated. The NSAID's such as ketorolac and antibiotics such as tobramycin are generally administered in an amount of about 1 to 2 drops per eye with drops containing about 25 microliters of formulation. The drops are generally administered 3 to 4 times per day.

EXAMPLE 6

In vitro rabbit corneal penetration of ketorolac was evaluated in the presence of tobramycin to determine if tobramycin alters penetration of ketorolac through rabbit corneas. Two sets of studies were performed to evaluate tobramycin's effect on ketorolac penetration.

Apparatus - A modified Franz diffusion cell consisting of an 8.0 ml glass receptor cell along with a teflon donor cell were used for the penetration experiments. A side arm allowed sampling of the receptor

phase. The donor cell was recessed to accommodate corneal curvature. A 0.3 ml volume of donor solution was placed on the epithelial side of the cornea, and evaporation of this donor solution was diminished by sealing a glass coverslip over the opening of the donor cell with silicon grease. To ensure corneal curvature throughout the course of the experiment, a 1.0 ml latex bulb was placed over the sampling port of the glass diffusion cell. By so doing, enough pressure was exerted under the cornea to maintain a curved, wrinkle-free membrane. Water at 37° C was circulated through the water jacket surrounding the receptor cell. A magnetic stir bar placed in the bottom of the receptor cell maintained homogeneity within the receptor solution.

Cornea Preparation - New Zealand white rabbits weighing 3.5 to 4 kg were used for the studies. Rabbits were sacrificed by rapid injection of 1.25 ml/kg of T-61 Euthanasia Solution (American Hoechst Corp. Animal Health Division, Somerville, NJ) into a marginal ear vein. The cornea were carefully removed along with 2-4 mm of surrounding scleral tissue then placed in a buffer containing: 0.57% sodium chloride, 0.361% sodium bicarbonate, 0.04% potassium chloride, 0.023% potassium phosphate dibasic, 0.007% magnesium sulfate, 0.08% calcium chloride, and 0.133% adenosine in water, adjusted to pH 7.4. This buffer was used as receptor solution for all studies; its selection was based on the ability to maintain corneal integrity throughout the diffusion studies.

Experimental Procedure - A fresh cornea was placed between the top and bottom of the teflon donor cell; this unit was then clamped onto the glass receptor cell. The receptor cell was filled with sterile, degassed buffer solution; all air bubbles were expelled from beneath the cornea by inverting the entire diffusion cell and

allowing bubbles to travel out the sampling port. After donor solution was placed on the cornea, a 0.3 ml sample of receptor solution was collected at the following time points: 15, 30, 45, 60 and 120 minutes. The 0.3 ml aliquot was replaced at each time point with fresh buffer solution.

Preparation of Test Solutions - 1. To determine ketorolac corneal diffusion in the presence of tobramycin, and to determine a dose effect, a saline vehicle was utilized to avoid potential complications by excipients. The following solutions were isotonic and prepared at pH 7.4: (a) 0.5% ketorolac tromethamine, 0.79% sodium chloride, purified water; (b) solution (a) with 0.15% tobramycin; (c) solution (a) with 0.30% tobramycin; and (d) solution (a) with 0.60% tobramycin.

2. To evaluate whether 0.30% tobramycin (a clinically acceptable and efficacious concentration) has an effect on ketorolac corneal diffusion when administered in a more complex vehicle, an isotonic solution at pH 7.4 was made which contained the following: (a) 0.5% ketorolac tromethamine, 0.79% sodium chloride, edetate disodium, benzalkonium chloride, purified water; (b) solution (a) with 0.30% tobramycin.

^{14}C-glycerol Penetration - To monitor corneal integrity throughout the course of the permeability studies, ^{14}C-glycerol penetration was evaluated (^{14}C-glycerol 15.76 mCi/mmole was obtained from NEN with a radiochemical purity of 98%). Nonionized ^{14}C-glycerol was incorporated into selected test solutions (1a and d, above). For controls, two additional isotonic test solutions were made at pH 7.4: (1) phosphate buffered saline; (2) 0.6% tobramycin in phosphate buffered saline. To a 2.0 ml aliquot of each test solution, 10 µl of ^{14}C-glycerol was added. At designated time intervals, 0.3 ml of receptor solution

was sampled for scintillation counting (Beckman model LS 8100).

Analytical Methods - 1. Quantitation of ketorolac was performed by HPLC. The mobile phase was composed of methanol, water and glacial acetic acid (65:34:1). The equipment included: a Spectra-Physics 8440 UV/Vis detector; a Spectra-Physics 4270 integrator; a Spectra-Physics 8700 solvent delivery system; a Dynatech autosampler; and a Whatman Partisil ODS 3, 10 micron column. The mobile phase flow rate was 1.0 ml/min; the sample injection volume was 50 µl; and the absorbance wavelength was 254 nm. A 100 µl aliquot of each sample was diluted with 150 µl of mobile phase.

2. Quantitation of tobramycin was performed using the Syva EMIT tobramycin assay kit. The assay is an enzyme immunoassay intended to quantitatively analyze tobramycin in human serum or plasma; the limit of detection is 1.0 µg/ml. The assay is based on competition for antibody sites between free drug in sample and drug labeled with glucose-6-phosphate dehydrogenase (G-6-P-DH). Since G-6-P-DH activity decreases upon binding with antibody, tobramycin concentration can be measured in terms of enzyme activity. Active enzyme converts oxidized nicotinamide adenine dinucleotide (NAD) to NADH. This conversion results in an absorbance change that is measured spectrophotometrically.

Each experiment was performed with matched controls; that is, from a single rabbit, one cornea was treated with a ketorolac (control) solution, and the other cornea was treated with the ketorolac and tobramycin solution. Each test solution containing tobramycin was evaluated in triplicate. For the study using the simple isotonic vehicle, data for nine control corneas were generated. Since these were control cornea, each is from a different

rabbit; hence, the deviation shown at each time point gives an indication of both the biological as well as experimental deviation inherent to this type of study.

An indication of corneal integrity throughout the course of these studies was determined by penetration of ^{14}C-glycerol. Changes in the permeability profile of ^{14}C-glycerol can be attributed to corneal alteration or damage. Select vehicles were chosen to evaluate whether corneal damage could be attributed to a particular compound or combination. With phosphate buffered saline serving as control, a two or three-fold increase in ^{14}C-glycerol penetration would indicate substantial corneal alteration. Table I shows that ^{14}C-glycerol penetration in a solution containing ketorolac tromethamine, or 0.6% tobramycin, or their combination, does not differ from its penetration in buffer alone. These results suggest that corneal integrity is not altered by ketorolac tromethamine or tobramycin.

TABLE I

Preparation	Percent of Initial Counts per Minute at 60 min	at 120 min
Phosphate Buffered Saline	2.10	7.36
Ketorolac tromethamine in Saline	2.47	8.60
Tobramycin (0.6%) in Phosphate buffered saline	1.83	7.08
Ketorolac tromethamine and Tobramycin (0.6%) in Saline	2.01	6.03

The average total milligrams of ketorolac penetrating the cornea at each time point for the simple solutions containing ketorolac alone and solutions

containing either 0.15%, 0.30% or 0.60% tobramycin, respectively, were compared. In all cases, the solutions containing tobramycin were equivalent to the control solution.

A comparison of the average total milligrams of ketorolac penetrating the cornea at each time point for the ophthalmic formulation with and without 0.30% tobramycin was made. Again, the test solution and the control solution were equivalent. Studies with the formulation demonstrated that after 60 minutes, there occurs a two to three fold increas in ketorolac diffusion, that is, enhanced penetration.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

WHAT IS CLAIMED IS:

1. An ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation, comprising:

an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment;

an ophtalmologically acceptable antibiotic in an effective amount for ophthalmic treatment;

a quaternary ammonium preservative;

a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant; and

an aqueous vehicle.

2. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 wherein said quaternary ammonium preservative is benzalkonium chloride.

3. The ophtalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 wherein said nonionic polyoxyethylated octylphenol surfactant is Octoxynol 40 and the antibiotic is tobramycin.

4. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 including disodium edetate.

5. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group: ketorolac, indomethacin, flurbiprofen, diclofenac, and suprofen.

6. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 5 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is ketorolac tromethamine.

7. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 1 comprising:

NSAID	0.001% to 10.0% wt/vol.;
Antibiotic	0.001% to 10.0% wt/vol.;
Preservative	0.001% to 1.0% wt/vol.;
Surfactant	0.001% to 1.0% wt/vol.; and
Purified Water	q.s. to 100%.

8. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 7 comprising:

ketorolac tromethamine	0.001% to 10.0% wt/vol.;
tobramycin	0.001% to 10.0% wt/vol.;
Preservative	0.001% to 1.0% wt/vol.;
Surfactant	0.001% to 1.0% wt/vol.; and
Purified Water	q.s. to 100%.

9. The ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 7 wherein said preservative is benzalkonium chloride, and the surfactant is Octoxynol 40.

10. The ophtalmologically acceptable non-steroidal anti-inflammatory drug formulation of

Claim 8, further comprising:

Chelating agent	0.01% to 1.0% wt/vol.;
Tonicifier	q.s. to achieve isotonicity with lacrimal fluid; and
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4%0.4.

11. The ophtalmologically acceptable non-steroidal anti-inflammatory drug formulation of Claim 9 comprising:

ketorolac tromethamine	0.50% wt/vol.;
Tobramycin	0.30% wt/vol.;
BAC (50% aq. soln.)	0.02% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
NaCl	0.18% wt/vol.;
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.
1N NaOH or 1N HCl	q.s. to adjust pH to 7.4%0.4; and
Purified Water	q.s. to 100%.

12. The use of a formulation comprising: an ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug in an effective amount for ophthalmic treatment, an antibiotic in an effective amount for ophthalmic treatment, a quaternary ammonium preservative, a stabilizing amount of a nonionic polyoxyethylated octylphenol surfactant, and an aqueous

vehicle for treating ophthalmic disease in a mammal suffering therewith.

13. The use of Claim 12 wherein said preservative is benzalkonium chloride and said surfactant is Octoxynol 40.

14. The use of Claim 12 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is selected from the group: ketorolac, indomethacin, flurbiprofen, diclofenac, and suprofen.

15. The use of Claim 12 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory carboxyl group-containing drug is Ketorolac Tromethamine and the antibiotic is tobramycin.

16. The use of Claim 15 wherein said ophthalmologically acceptable non-steroidal anti-inflammatory drug formulation comprises:

ketorolac tromethamine	0.50% wt/vol.;
Tobramycin	0.30% wt/vol.;
BAC (50% aq. soln.)	0.01% wt/vol.;
Octoxynol 40 (70% aq. soln.)	0.01% wt/vol.;
EDTA Na_2	0.10% wt/vol.;
NaCl	0.18% wt/vol.;
Boric Acid	0.9% wt/vol.
Na Borate	0.45% wt/vol.
1N NaOH or 1N HCl	to adjust pH to 7.4±0.4; and
Purified Water	q.s. to 100%.

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